Macroscopic Type Is a Prognostic Factor for Recurrence-free Survival After Resection of Gastric GIST

HIROSHI MIYAMOTO[1], CHIKARA KUNISAKI[2], YUICHI OTSUKA[3], MASAZUMI TAKAHASHI[4], RYO TAKAGAWA[5], KOICHIRO MISUTA[6], KUNIO KAMEDA[7], HIROCHIKA MAKINO[1], GORO MATSUDA[8], NAOTAKA YAMAGUCHI[9], NORIYUKI KAMIYA[10], TAKASHI MURAKAMI[11], SATOSHI MORITA[12], HIROTOSHI AKIYAMA[1] and ITARU ENDO[1]

Departments of [1]Gastroenterological Surgery and [12]Biostatistics and Epidemiology, Yokohama City University Graduate School of Medicine, Yokohama, Japan;
[2]Department of Surgery, Gastroenterological Center, Yokohama City University, Yokohama, Japan;
[3]Department of Surgery, Kanto Medical Center NTT E.C., Tokyo, Japan;
[4]Department of Surgery, Yokohama City Hospital, Yokohama, Japan;
[5]Department of Surgery, Yokosuka Kyosai Hospital, Yokosuka, Japan;
[6]Department of Surgery, Fujisawa City Hospital, Fujisawa, Japan;
[7]Department of Surgery, Yokosuka City Hospital, Yokosuka, Japan;
[8]Department of Surgery, National Hospital Organization Yokohama Medical Center, Yokohama, Japan;
[9]Department of Surgery, Yokohama-City Minato Red Cross Hospital, Yokohama, Japan;
[10]Department of Surgery, Ito Municipal Hospital, Ito, Japan;
[11]Department of Surgery, Yokohama Ekisaikai Hospital, Yokohama, Japan

Abstract. *Background: Accurate evaluation of the biological behavior of Gastrointestinal stromal tumor and careful selection of patients with a high risk for tumor recurrence are necessary. In the present study, we analyzed prognostic factors in patients with GIST. Patients and Methods: A total of 214 patients who had undergone curative resection of a localized primary gastric GIST without adjuvant therapy were enrolled in this retrospective study. Prognostic factors were analyzed. The growth pattern was classified as intramural, endoluminal, exoluminal, or mixed- type. Results: On univariate and multivariate analyses, recurrence was predicted by exoluminal or mixed-type (hazard ratio [HR]=3.7, p=0.043), tumor size of >3.5 cm (HR=7.1, p=0.01), and mitotic rate of >5/50 high-power fields (HR=7.9, p<0.001). Conclusion: It is suggested that exoluminal or mixed-type is independently associated with recurrence of surgically resected gastric GIST in addition to tumor size and mitotic rate.*

Correspondence to: Dr. Hiroshi Miyamoto, Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan. E-mail: yo-chan.634@nifty.com

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Gastrointestinal stromal tumor (GIST) is the most common type of mesenchymal tumor of the gastrointestinal tract (1). It commonly contains a mutation in the *KIT* proto-oncogene or, less frequently, in platelet-derived growth factor receptor-alpha (PDGFR-α). GISTs occur at any site along the tubular gastrointestinal tract from the esophagus to the rectum, but they are more common in the stomach (60%-70%) (1). Gastric GIST generally has a more favorable clinical course than small intestinal GIST; thus, location relates to the prognosis (2-6). The 5- and 10-year overall survival rates for patients who undergo curative resection for non-metastatic primary disease of gastric GIST are 93% and 88%, respectively (4).

Management at initial diagnosis and treatment of gastric GIST have been active areas of research during the last 10 years. The gold standard for localized primary gastric GIST is surgical resection (6, 7). Many gastric GISTs, with the possible exception of very small (<1 cm) incidentally found tumors, seem to have the potential to recur after surgical resection (1, 6, 7). However, risk factors for recurrence in the liver, peritoneum, and other sites are unclear.

The aim of the present study was to determine the impact of clinicopathological factors on recurrence in a series of surgically resected gastric GISTs treated in Japanese multi-Institutions.

Table I. *Clinicopathological characteristics of patients with gastric GIST.*

Variable	Patients (n=214)
Gender	
Men	112 (52%)
Women	102 (48%)
Age (years)	
Mean (range), Median	65.1 (28-90), 67
Portion	
U	108 (50%)
M	80 (37%)
L	26 (13%)
Macroscopic growth pattern	
Intramural	49 (23%)
Endoluminal	61 (28%)
Exoluminal	71 (33%)
Mixed	33 (16%)
Tumor size	
Mean (range), Median, cm	4.1 (0.2-21.0), 3.5
Mitotic rate	
<5/50 HPF	161 (75%)
≥5/50 HPF	53 (25%)

GIST: gastrointestinal stromal tumor, HPF: high power fields. U: upper third, M: middle third, L: lower third.

Patients and Methods

Patients and diagnosis. Between February 1991 and August 2010, 225 patients underwent potentially curative resection of a localized primary gastric GIST at the Yokohama Clinical Oncology Group's Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine and its affiliated institutions. All patients with the exception of 11, who underwent adjuvant treatment, were enrolled.

The diagnosis of GIST was confirmed by positive staining for KIT (CD117) protein and/or CD34 as assessed by immunohistochemical staining regardless of myogenic and neurogenic markers,. None of the patients received adjuvant treatment. Postoperative follow-up comprised physical examination, computed tomography, and gastrointestinal endoscopy.

Analysis of clinicopathologic parameters. The following clinicopathologic factors were analyzed: sex, age, tumor site, growth pattern, tumor size, and mitotic rate. The portion of the primary tumor was classified as upper third (U), middle third (M), or lower third (L). The macroscopic growth pattern was classified as intramural, endoluminal, exoluminal, or mixed type according to Skandalakis' classification (8). Tumor size was defined by maximum diameter and classified into two groups: >3.5 and ≤3.5 cm (the median tumor size was 3.5 cm). The mitotic rate was determined by counting the number of mitotic figures per 50 high-power fields (HPF) and categorized as ≤5 or >5/50 HPF. Recurrence-free survival (RFS) was defined as the time from initial diagnosis to the time of first recurrence or tumor-related death.

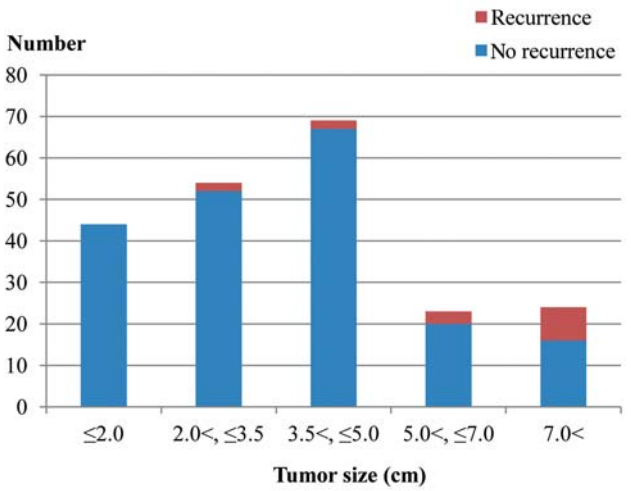

Figure 1. *Recurrence rate according to tumor size, which was classified with different cut-off values: 2.0, 3.5, 5.0, and 7.0 cm.*

Statistical analysis. For statistical analysis, qualitative data are presented as numbers (%). Continuous variables are expressed as median with minimum and maximum values. Categorical variables were compared by the chi-square test. The Kruskal-Wallis test was used to compare data among more than two groups. Actuarial Recurrence-free survival (RFS) from the date of surgical resection was calculated using the Kaplan-Meier method. The relation of characteristics to outcome was tested by univariate log-rank analysis. Variables that were significant in univariate analysis were entered into multivariate analysis. Multivariate analysis was performed with the Cox proportional hazards regression model. The SPSS version 18 software (Link or supplier) was used in all analyses, and the level of significance was set at $p<0.05$.

Results

Clinicopathological characteristics. Clinicopathological characteristics of patients are displayed in Table I. The median age of the patients was 67 years (range=28–90 years), and the ratio of males to females was almost 50:50. The number of tumor sites was greatest in the upper portion. The number of patients with an endoluminal or exoluminal growth pattern was greater than the number of patients with other growth patterns. The median tumor size was 3.5 cm (range=0.2–21 cm). Most patients (161, 75%) had a mitotic rate of ≤5/50 HPF.

Partial gastrectomy, the most common procedure, was performed in 184 patients (86%), 33 (18%) of whom underwent laparoscopic gastrectomy. Two patients underwent pancreaticoduodenectomy, 2 underwent esophagectomy, 9 underwent distal gastrectomy, 16 underwent proximal gastrectomy, and 1 underwent total gastrectomy. No perioperative mortality was observed. Perioperative morbidity

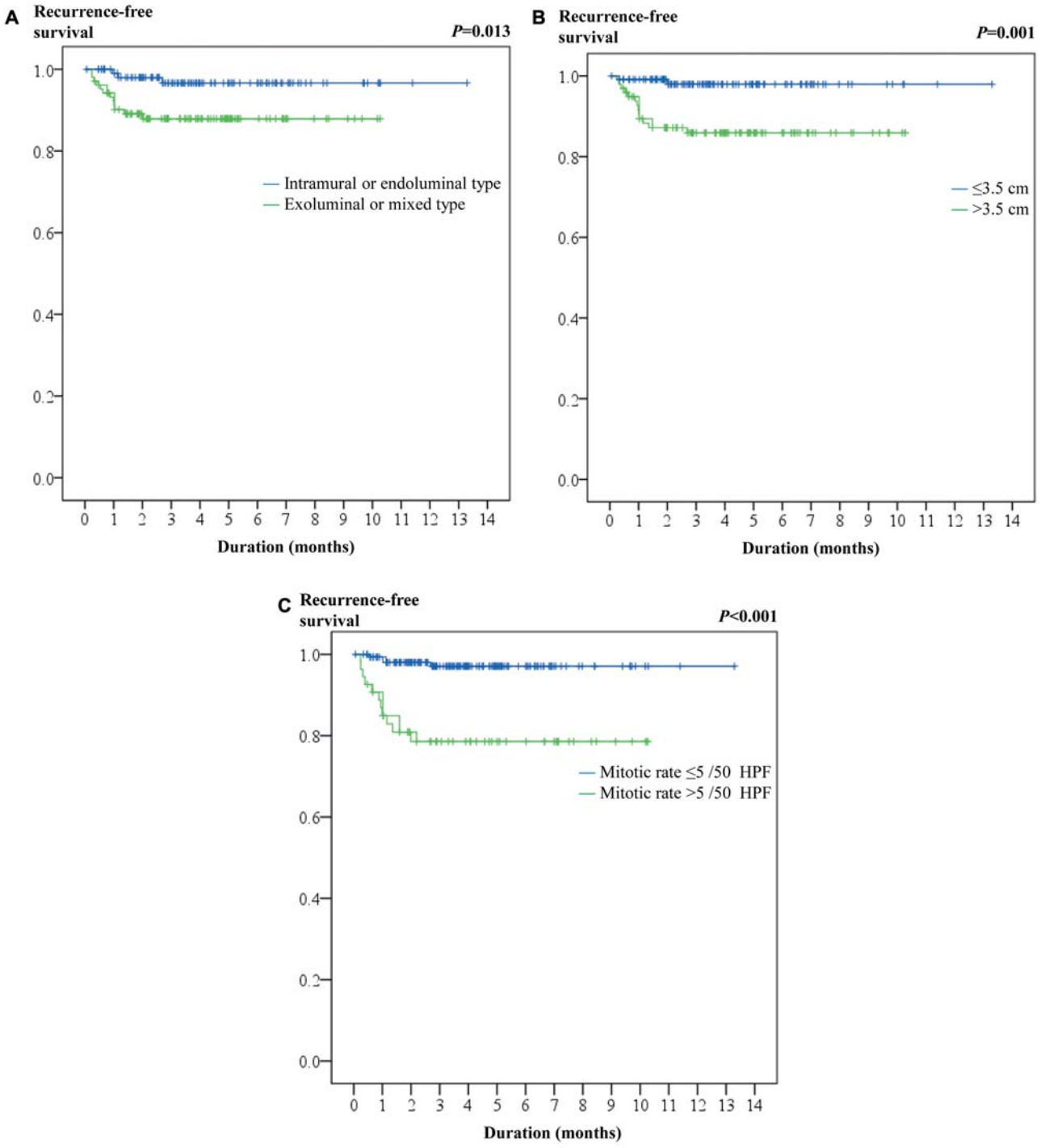

Figure 2. *A: Recurrence-free survival based on macroscopic growth pattern. B: Recurrence-free survival based on tumor size. Cut-off value was 3.5 cm. C: Recurrence-free survival based on mitotic rate.*

occurred in 15 patients (7%) and included pancreatic fistula in 5, surgical site infection in 2, anastomotic leakage in 2, ileus in 1, pneumonia in 1, enteritis in 1, drug eruption in 1, cholangitis in 1, and hepatic infarction in 1.

Long-term outcome. At a median follow-up of 3.6 years after resection of the primary tumor, 188 patients were alive without disease. Recurrence occurred in 15 patients; 4 died of this disease, 11 were alive with disease, and 11 died of

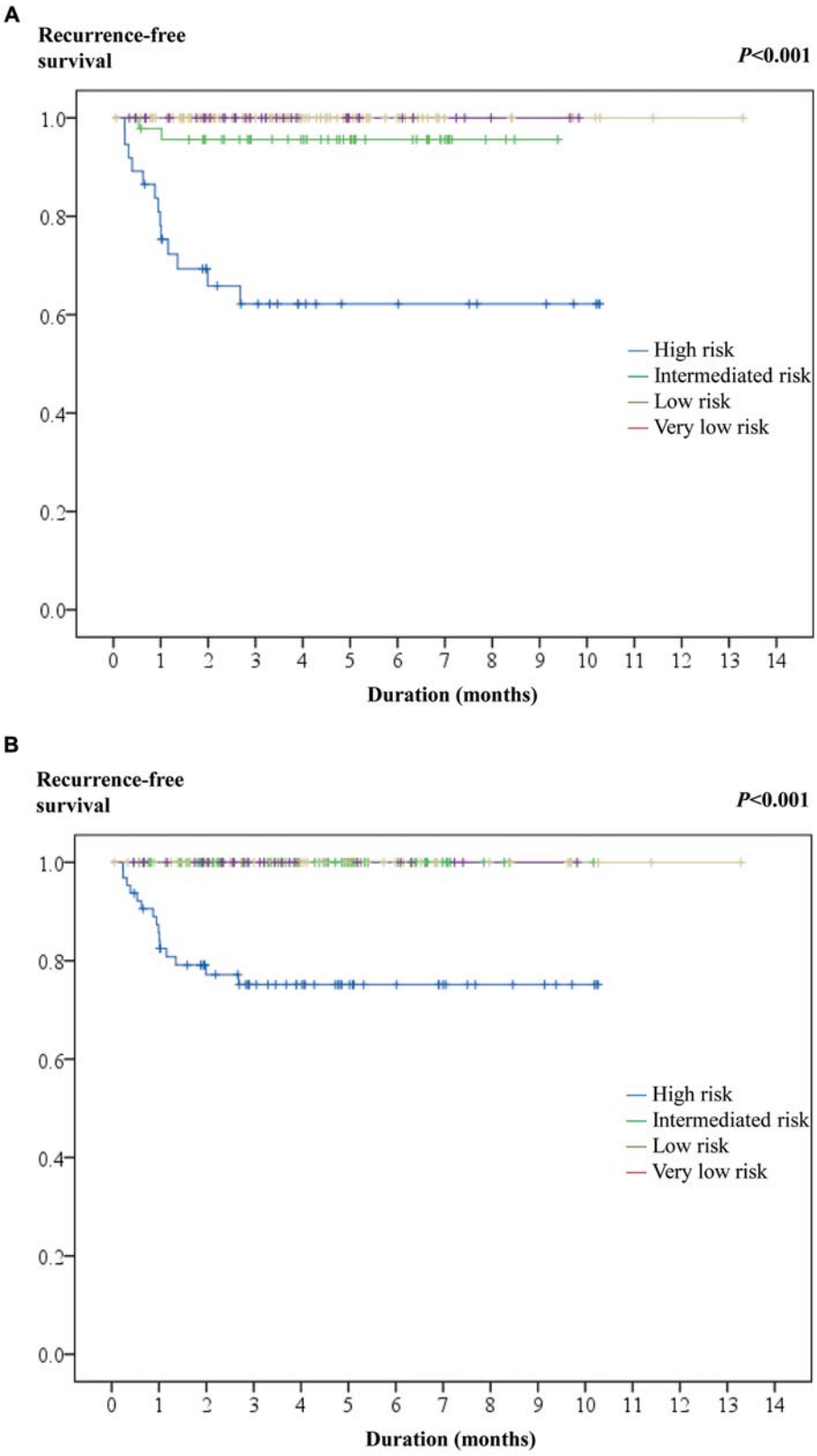

Figure 3. *A: Recurrence-free survival according to the NIH criteria; B: Recurrence-free survival according to the modified risk classification in terms of the NIH criteria. The modified risk classification was defined the risk classification is raised one step when a patient has exoluminal or mixed type.*

Table II. *Predictors of recurrence after resection of gastric GIST in 214 patients.*

Variable	No.	RFS at 1 year (%)	RFS at 2 year (%)	RFS at 5 year (%)	Univariate *p*-Value	Multivariate *p*-Value	Hazard ratio (95% CI)
Exoluminal or mixed	104	93	89	87	0.013	0.043	3.7
Intramural or endoluminal	110	99	98	96			(1.0-13.1)
Tumor size >3.5 cm	98	94	89	84	0.001	0.01	7.1
Tumor size ≤3.5 cm	116	99	98	98			(1.6-31.5)
Mitotic rate ≥5/50 HPF	53	91	81	79	<0.001	<0.001	7.9
Mitotic rate <5/50 HPF	161	99	98	98			(2.5-24.7)

GIST: Gastrointestinal stromal tumor, RFS: recurrence-free survival, CI: confidence intervals, HPF: high power field.

other causes. The recurrence site included the liver in eight patients, peritoneum in five, local in one, and bone in one. The 1-, 2-, and 5-year RFS was 95%, 93%, and 92%, respectively.

Sex, age, and tumor site did not predict recurrence. The recurrence rate was analyzed according to tumor size, which was classified with different cut-off values: 2.0, 3.5, 5.0, and 7.0 cm (Figure 1). Tumor size was classified into two groups with each cut-off value and analyzed with univariate analysis. There were significant differences among 3.5 cm (p=0.001), 5.0 cm (p<0.001), and 7.0 cm (p<0.001) tumors. Intraoperative tumor rupture occurred in two patients, and lymph node metastasis occurred in three patients; there was no recurrence in any of these five patients.

On univariate analysis, exoluminal or mixed-type, tumor size of >3.5 cm, and mitotic rate of >5/50 HPF were significantly correlated with a poor prognosis (Table II, Figure 2A-C).

On multivariate analysis, factors independently associated with recurrence were exoluminal or mixed-type, tumor size of >3.5 cm, and mitotic rate of >5/50 HPF (Table II).

Discussion

This retrospective study evaluated the prognostic factors of growth pattern for the clinical outcome of patients with gastric GIST. We demonstrated that macroscopic features such as exoluminal or mixed-type were negative prognostic factors, as were tumor size and mitotic rate. To the best of our knowledge, this is the first report showing that an exclusive focus on the macroscopic growth pattern in gastric GIST, which generally has a more favorable clinical course than does small intestinal GIST, appears to be of significant prognostic impact only for gastric GIST.

Several large series of completely resected gastric GIST have identified tumor size and tumor mitotic rate as prognostic factors, but no information on macroscopic type was available (9-14).

The most commonly used scheme to assess the risk of recurrence is the National Institutes of Health (NIH) consensus criteria (so-called Fletcher's criteria), which are based on primary tumor diameter and mitotic rate per 50 HPF. Tumor size and mitotic rate were used as the sole parameters for defining eight prognostic categories that were sub-divided into four risk groups (9). Since it was initially put forth, the NIH model has been shown to be accurate in predicting biological characteristics of tumors (15-17). A second proposed system, offered by the Armed Forces Institute of Pathology (AFIP) criteria (so-called Miettinen's criteria), further differentiates risk based on size, mitotic rate, and gastric *versus* non-gastric primary tumors (5, 18-20). This risk system is distinguished from the NIH system by taking into consideration the anatomic site of the tumor. Initially defining the eight prognostic sub-groups based on size and mitotic rate, Miettinen *et al*. added the anatomic site to separate the four risk groups.

Although the size of 5 cm has been adopted as a cut-off value for defining low *versus* non-low risk in the NIH and AFIP systems, univariate and multivariate analyses indicated that a size of >3.5 cm seemed to be associated with increased recurrence in this study. A size of 3.5 cm was adopted as a cut-off value and is smaller than the cut-off value in the NIH and AFIP systems. Two patients (0.9%) whose tumor size was 3.5 to 5 cm developed recurrence. The mitotic rate is also well-known to be predictive of recurrence and survival (13, 21). It is generally considered that <5 mitoses per 50 HPF constitute low risk (14, 18-20, 22-24). In our study, the risk of recurrence, in terms of mitotic rate, was similar to that reported previously (25, 26). A mitotic rate of >5/50 HPF is also significantly correlated with a poor prognosis. We reconfirmed the prognostic value of tumor size and mitotic index.

In the present study, exoluminal or mixed-type was significantly correlated with a poor prognosis by univariate and multivariate analyses. Some studies reported that patients with a primary GIST treated for spontaneous tumor rupture or with rupture that occurred during surgery have a very high

risk of tumor recurrence (27). A large study recently reported that large tumor size, high mitotic count, non-gastric location, and occurrence of rupture are independent adverse prognostic factors (28). Although there was no recurrence in patients in whom rupture occurred during surgery, it is difficult to clarify the relationship between tumor rupture and prognosis because tumor rupture occurred in only two patients in this study.

A few studies have examined the macroscopic growth pattern, but whether recurrence is predicted by the growth pattern was uncertain (29). Some studies have shown that the presence of serosal penetration is an adverse prognostic factor for GIST (30) and that extramural growth is a predictor of peritoneal recurrence in GIST (31). However, these studies included not only gastric GIST, but also other primary lesions. In this study, four out of five patients in whom peritoneal recurrence occurred had exoluminal or mixed-type tumors. Therefore, it seems that the exoluminal or mixed-type has a strong relationship with peritoneal recurrence and results in a worse prognosis. It is suggested that peritoneal recurrence was probably induced as a consequence of microscopic serosal penetration and microscopic rupture. It is likely that such tumors have minor serosal defects or microscopic tears related either to spontaneous mobility of the tumors or mobility caused by surgical manipulation (31). Thus, it is necessary to be especially careful of recurrence in patients with the exoluminal or mixed-type, and these patients might be candidates for adjuvant tyrosine kinase inhibitor therapy.

Three patients, who were classified as having intermediate risk according to NIH, experienced recurrence, and all patients had the exoluminal or mixed type. When a patient has an exoluminal or mixed type tumor, we recommend that the risk classification should be raised one step. In terms of the NIH criteria, all patients who experienced recurrence were classified as high-risk according to the modified risk classification (Figure 3A, B). In the future, it is necessary to confirm the prognostic impact of the macroscopic growth pattern of GIST in larger prospective studies as the present study was retrospective in nature.

In conclusion, factors independently associated with recurrence of gastric GIST were exoluminal or mixed-type, a tumor size of >3.5 cm, and a mitotic rate of >5/50 HP in surgically resected primary gastric GISTs in the absence of therapy with tyrosine kinase inhibitors. It is suggested that exoluminal or mixed-type is independently associated with peritoneal recurrence of surgically resected gastric GISTs. It is necessary to accumulate larger numbers of patients to establish the prognostic factors of growth patterns.

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References

1 Miettinen M and Lasota J: Gastrointestinal stromal tumors: pathology and prognosis at different sites. Seminars in diagnostic pathology *23*: 70-83, 2006.

2 Emory TS, Sobin LH, Lukes L, Lee DH and O'Leary TJ: Prognosis of gastrointestinal smooth-muscle (stromal) tumors: dependence on anatomic site. The American journal of surgical pathology *23*: 82-87, 1999.

3 Crosby JA, Catton CN, Davis A, Couture J, O'Sullivan B, Kandel R and Swallow CJ: Malignant gastrointestinal stromal tumors of the small intestine: a review of 50 cases from a prospective database. Annals of surgical oncology *8*: 50-59, 2001.

4 Fujimoto Y, Nakanishi Y, Yoshimura K, and Shimoda T: Clinicopathologic study of primary malignant gastrointestinal stromal tumor of the stomach, with special reference to prognostic factors: analysis of results in 140 surgically resected patients. Gastric cancer : official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association *6*: 39-48, 2003.

5 Miettinen M, Sobin LH, and Lasota J: Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. The American journal of surgical pathology *29*: 52-68, 2005.

6 Lasota J, Stachura J, and Miettinen M: GISTs with PDGFRA exon 14 mutations represent subset of clinically favorable gastric tumors with epithelioid morphology. Laboratory investigation; a journal of technical methods and pathology *86*: 94-100, 2006.

7 DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, and Brennan MF: Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Annals of surgery *231*: 51-58, 2000.

8 Skandalakis JE, Gray SW and Shepard D: Smooth muscle tumors of the stomach. International abstracts of surgery *110*: 209-226, 1960.

9 Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH and Weiss SW: Diagnosis of gastrointestinal stromal tumors: A consensus approach. Human pathology *33*: 459-465, 2002.

10 Martin J, Poveda A, Llombart-Bosch A, Ramos R, Lopez-Guerrero JA, Garcia del Muro J, Maurel J, Calabuig S, Gutierrez A, Gonzalez de Sande JL, Martinez J, De Juan A, Lainez N, Losa F, Alija V, Escudero P, Casado A, Garcia P, Blanco R, and Buesa JM: Deletions affecting codons 557-558 of the c-KIT gene indicate a poor prognosis in patients with completely resected gastrointestinal stromal tumors: a study by the Spanish Group for Sarcoma Research (GEIS). Journal of clinical oncology: official journal of the American Society of Clinical Oncology *23*: 6190-6198, 2005.

11 Bumming P, Ahlman H, Andersson J, Meis-Kindblom JM, Kindblom LG, and Nilsson B: Population-based study of the diagnosis and treatment of gastrointestinal stromal tumours. The British journal of surgery *93*: 836-843, 2006.

12 Wu TJ, Lee LY, Yeh CN, Wu PY, Chao TC, Hwang TL, Jan YY, and Chen MF: Surgical treatment and prognostic analysis for gastrointestinal stromal tumors (GISTs) of the small intestine: before the era of imatinib mesylate. BMC gastroenterology *6*: 29, 2006.

13 Dematteo RP, Gold JS, Saran L, Gonen M, Liau KH, Maki RG, Singer S, Besmer P, Brennan MF, and Antonescu CR: Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). Cancer *112*: 608-615, 2008.
14 Cao H, Zhang Y, Wang M, Shen DP, Sheng ZY, Ni XZ, Wu ZY, Liu Q, Shen YY, and Song YY: Prognostic analysis of patients with gastrointestinal stromal tumors: a single unit experience with surgical treatment of primary disease. Chinese medical journal *123*: 131-136, 2010.
15 Rutkowski P, Nowecki ZI, Michej W, Debiec-Rychter M, Wozniak A, Limon J, Siedlecki J, Grzesiakowska U, Kakol M, Osuch C, Polkowski M, Gluszek S, Zurawski Z, and Ruka W: Risk criteria and prognostic factors for predicting recurrences after resection of primary gastrointestinal stromal tumor. Annals of surgical oncology *14*: 2018-2027, 2007.
16 Steigen SE, Bjerkehagen B, Haugland HK, Nordrum IS, Loberg EM, Isaksen V, Eide TJ, and Nielsen TO: Diagnostic and prognostic markers for gastrointestinal stromal tumors in Norway. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc *21*: 46-53, 2008.
17 Agaimy A: Gastrointestinal stromal tumors (GIST) from risk stratification systems to the new TNM proposal: more questions than answers? A review emphasizing the need for a standardized GIST reporting. International journal of clinical and experimental pathology *3*: 461-471, 2010.
18 Miettinen M, El-Rifai W, L HLS, and Lasota J: Evaluation of malignancy and prognosis of gastrointestinal stromal tumors: a review. Human pathology *33*: 478-483, 2002.
19 Miettinen M and Lasota J: Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Archives of pathology & laboratory medicine *130*: 1466-1478, 2006.
20 Miettinen M, Makhlouf H, Sobin LH, and Lasota J: Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. The American journal of surgical pathology *30*: 477-489, 2006.
21 Moral Moral G, Gil Piedra F, Velasco Oses A, Seco Gil JL, de la Plaza Galindo M, and Santamaria Garcia JL: Stromal tumors of the digestive tract. Prognostic value of mitotic index. Revista espanola de enfermedades digestivas: organo oficial de la Sociedad Espanola de Patologia Digestiva *90*: 335-344, 1998.
22 Wong NA, Young R, Malcomson RD, Nayar AG, Jamieson LA, Save VE, Carey FA, Brewster DH, Han C, and Al-Nafussi A: Prognostic indicators for gastrointestinal stromal tumours: a clinicopathological and immunohistochemical study of 108 resected cases of the stomach. Histopathology *43*: 118-126, 2003.
23 Woodall CE, 3rd, Brock GN, Fan J, Byam JA, Scoggins CR, McMasters KM, and Martin RC, 2nd: An evaluation of 2537 gastrointestinal stromal tumors for a proposed clinical staging system. Archives of surgery (Chicago, I ll: 1960) *144*: 670-678, 2009.
24 Gold JS, Gonen M, Gutierrez A, Broto JM, Garcia-del-Muro X, Smyrk TC, Maki RG, Singer S, Brennan MF, Antonescu CR, Donohue JH, and DeMatteo RP: Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. The lancet oncology *10*: 1045-1052, 2009.
25 Zhang XH, He YL, Zhan WH, Cai SR, and Zhang CH: Diagnosis and treatment of gastrointestinal stromal tumors: report of 135 cases. Zhonghua wei chang wai ke za zhi=Chinese journal of gastrointestinal surgery *10*: 17-20, 2007.
26 Trent JC and Benjamin RS: New developments in gastrointestinal stromal tumor. Current opinion in oncology *18*: 386-395, 2006.
27 Hohenberger P, Ronellenfitsch U, Oladeji O, Pink D, Strobel P, Wardelmann E, and Reichardt P: Pattern of recurrence in patients with ruptured primary gastrointestinal stromal tumour. The British journal of surgery *97*: 1854-1859, 2010.
28 Joensuu H, Vehtari A, Riihimaki J, Nishida T, Steigen SE, Brabec P, Plank L, Nilsson B, Cirilli C, Braconi C, Bordoni A, Magnusson MK, Linke Z, Sufliarsky J, Federico M, Jonasson JG, Dei Tos AP, and Rutkowski P: Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. The lancet oncology *13*: 265-274, 2012.
29 Yokoi K, Tanaka N, Shoji K, Ishikawa N, Seya T, Horiba K, Kanazawa Y, Yamashita K, Ohaki Y, and Tajiri T: A study of histopathological assessment criteria for assessing malignancy of gastrointestinal stromal tumor, from a clinical standpoint. Journal of gastroenterology *40*: 467-473, 2005.
30 Vallbohmer D, Marcus HE, Baldus SE, Brabender J, Drebber U, Metzger R, Holscher AH, and Schneider PM: Serosal penetration is an important prognostic factor for gastrointestinal stromal tumors. Oncology reports *20*: 779-783, 2008.
31 Agaimy A, Vassos N, Wunsch PH, Hohenberger W, Hartmann A, and Croner RS: Impact of serosal involvement/extramural growth on the risk of synchronous and metachronous peritoneal spread in gastrointestinal stromal tumors: proposal for a macroscopic classification of GIST. International journal of clinical and experimental pathology *5*: 12-22, 2012.

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